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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,935	04/27/2001	Alexander Munishkin	Q01/08C	4219

7590 04/08/2003

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/844,935	Muniskin
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Mar 4, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached sheet

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: _____

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ .

10. ☐ Other:

Claims 1-5, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995).

Marsh et al. teaches a method of determining the presence or absence of a target molecule (abstract) comprising the steps of:

a) providing a first RNA molecule which can bind to a target molecule and has the formula:

5'-A-B-C-D-E-3'; (Figure 1, 2 and 4)

wherein A is a section of the RNA molecule having 10-10,000 nucleotides which section is, with another sequence, E, replicated by an RNA replicase, the letter "B" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another sequence D, binds the target molecule under binding conditions, the letter "C" denotes a section of the RNA molecule having approximately 1 to 10000 nucleotides, the letter "D" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another B, binds the target molecule under binding conditions, the section B and D, in combination, comprise in total at least 10 nucleotides, the first RNA molecule, with sections B and D bound to target, is acted upon by the RNA replicase to form a second RNA molecule, said second RNA molecule has the following formula:

5'-E'-X-A'-3';

wherein, E' is the complement to E, and A' is the complement to A, and the letter "X" denotes the complement of parts of the sections B and D which may be replicated, or the letter denotes the direct bond between sections E' and A', and second RNA molecule is replicated by the RNA replicase under replicating conditions and combining first RNA molecule with a sample (Figure 1, 2, 3 and 4 and Materials and Methods, page 983, lines 12-25);

b) imposing binding conditions on a sample potentially containing target molecules in the presence of first RNA molecule, in the presence of the target molecule, first RNA molecules forms a target-first RNA molecule complex to form a first modified sample (Figure 2, 3 and 4);

c) imposing RNA replicase reaction conditions on the first modified sample, in the presence of an RNA replicase, to form second RNA molecule in the presence of target to make a second modified sample (Materials and Methods, page 983, lines 12-25);

d) monitoring second modified sample for the presence of the second RNA molecule or its complement, which presence or absence is indicative of the presence or absence of the target molecule (Materials and Methods, page 983, lines 25-32 and Table 1).

Marsh et al. teaches that section "C" may serve as a non base-paired spacer to facilitate access of the replicase to the promoter (page 990, lines 9-10).

Claims 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995) in view of Spiegelman (U.S. Patent 3,444,043) (May 13, 1969).

Marsh et al teaches a composition of claims 1-5, and 7 as described above.

Marsh et al. does not teach a composition by providing paired RNA molecules.

Marsh et al does not teach section "C" of the RNA molecule which section is capable of preventing the replication of the first molecule by the RNA replicase (abstract and column 7, lines 8-44).

Spiegelman teaches the customized preparation of RNA templates as he states, "An RNA template of an in vitro replicating system may be formed in situ. If one were, for example, to introduce foreign bases or nucleotides (e.g., analogues of known bases or nucleotides) into the replicating system, a mutant may be formed which would be the biologically active template for

replication with those same bases or nucleotides, in such instances, one would be synthesizing mutants in vitro in a known way (Column 5, lines 1-8)".

Spiegelman teaches section "C" of the RNA molecule which section is capable preventing the replication of the first molecule by the RNA replicase (abstract and column 7, lines 8-44).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute RNA template model of Spiegelman as the identification of target molecule in the method of Marsh et al., since Spiegelman et al. states "There is good evidence that the replicase recognizes the particular sequence of nucleotides at the beginning and at the end of the biologically active viral RNA template during the course of the replication. It is inferred from this recognition pattern that the intermediate portion of the RNA template is not essential to the direction of or instruction found in the replication mechanism studied. This suggests that the recognition sequences of nucleotides present at the beginning and end of a biologically active RNA template molecule can be selectively bonded to otherwise non-biologically active or non-viral RNA to produce a synthesized biologically active RNA product. It is thought that the RNA forms a circle and these two recognition sequences of the molecule overlap each other to provide double-stranded regions: such overlapped regions could afford, therefore, identification of the RNA molecule in a single, rapid scanning process (Column 4, lines 59-75)". An ordinary practitioner would have been motivated to combine the model of custom made RNA template of Spiegelman into the method of Marsh et al. in order to achieve the express advantages noted by Spiegelman of a method which can provide identification of the RNA molecule in a single, rapid scanning process.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995) in view of Stratagene Catalog (1988,

Page 39).

Marsh et al. teach the compositions of claims 1-5, and 7 as described above in detail.

Marsh et al. do not teach the motivation to combine all the reagents for detecting an analyte in a sample in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of claims 1-5, and 7 of Marsh et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control (page 39, column 1).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995) in view of Spiegelman (U.S. Patent 3,444,043) (May 13, 1969) further in view of Stratagene Catalog (1988, Page 39).

Marsh et al. in view of Spiegelman expressly teach the method claims and assay reagents of claims 8 as described above in detail.

Marsh et al. in view of Spiegelman do not teach the motivation to combine all the reagents for detecting an analyte in a sample in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the composition of Marsh et al. in view of Spiegelman into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control (page 39, column 1).

Response to Arguments

Applicant's arguments filed on March 4, 2003, have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re*

Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Spiegelman et al. since Spiegelman et al. states "There is good evidence that the replicase recognizes the particular sequence of nucleotides at the beginning and at the end of the biologically active viral RNA template during the course of the replication. It is inferred from this recognition pattern that the intermediate portion of the RNA template is not essential to the direction of or instruction found in the replication mechanism studied. This suggests that the recognition sequences of nucleotides present at the beginning and end of a biologically active RNA template molecule can be selectively bonded to otherwise non-biologically active or non-viral RNA to produce a synthesized biologically active RNA product. It is thought that the RNA forms a circle and these two recognition sequences of the molecule overlap each other to provide double-stranded regions: such overlapped regions could afford, therefore, identification of the RNA molecule in a single, rapid scanning process (Column 4, lines 59-75)". The same logic is applicable to other 103(a) references as well.

Applicant argues to withdraw the 102(b) rejections because Marsh does not teach some characteristic features of use of the composition of the instant invention. This argument is not persuasive. In response to applicant's argument that , a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this case, Marsh clearly teaches that section "C" may serve as a non base-paired spacer to facilitate access of the replicase to the promoter (page 990, lines 9-10). In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re*

Casey, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Applicant argues to withdraw the 102(b) and 103(a) rejections because Marsh and Spiegelman do not teach some characteristic features of the instant invention. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., (I) the replicated strand is a different sequence (ii) applicant's claimed invention is not a mutation, and (iii) any specific type of single, rapid screening process) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant then argues the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the "lacks a reasonable expectation of success." argument, The MPEP 2143.02 states ,"Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context

of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Marsh references of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different imposing RNA replicase reaction conditions on the first modified sample, in the presence of an RNA replicase, to form second RNA molecule in the presence of target to make a second modified sample (Materials and Methods, page 983, lines 12-25), were actually experimentally studied and found to be functional. This evidence of functionality trumps the attorney arguments, which argues that Marsh and Spiegelman references are an invitation to research, since Marsh steps beyond research and shows the functional product.

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